

# Carcinoembryonic Antigen (CEA) Plasma Levels in Michigan and Wisconsin Dairy Farmers

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Carcinogenic embryonic antigen (CEA) titers were determined for 611 Michigan farmers exposed to PBB and a control nonexposed population of 138 Wisconsin farmers.

The overall prevalence of elevated CEA titers was slightly higher in the Michigan study group, but the difference was not statistically significant. Smoking and/or significant past or present conditions (inflammatory bowel disease, ulcers, polyps, liver disease, chronic lung disease, or malignancies) were found to result in higher prevalence of elevated CEA titers, in both the Michigan study group and the Wisconsin control group, thus confirming previous reports.

In addition, serum PBB concentrations appeared to be positively correlated with CEA titers. The possibility that the effect of PBB may be additive to that of other factors which are known to result in an increased prevalence of elevated CEA titers is discussed.

Carcinoembryonic antigen (CEA), when first isolated and characterized in 1965 (1), was considered to be a specific marker for entodermally derived tumors. Additional investigations found elevated titers in a broad spectrum of both malignant (2-4) and nonmalignant conditions (5-7). The potential of CEA as a method for quick, noninvasive mass screening for gastrointestinal tract tumors was found to be limited because it soon appeared that CEA reflected active disease processes of many types, not only malignant ones. It is currently felt that CEA represents a nonspecific material resulting from pathological cell changes which may occur in a variety of tissues and may reflect the state of cell de-differentiation. Clinically, CEA is used to monitor cancer therapy results and as evidence for early tumor recurrence of malignancies which have been identified as producing CEA. Serial CEA titers are used in such cases.

Whether an elevated CEA titer represents an increased risk of having an undiagnosed illness or an

increased risk of developing an illness is under investigation. One study has provided a suggestion that this may be the case (8). As part of an on-going collaborative study with Hoffmann-LaRoche scientists, the Environmental Sciences Laboratory is evaluating CEA titers as possible indicators of health risk, especially in occupational groups known or suspected of having toxic or carcinogenic exposures.

The lack of organ system specificity of CEA possibly can be used to advantage. Different tissues may be producing CEA independently and the resulting titer could represent a summation of the effects of one toxic agent on several sites, or several agents affecting the same or different organ systems. In this sense, CEA might represent an index of multiple factor interaction. Environmental factors such as cigarette smoking, excessive alcohol consumption, and occupational exposure to vinyl chloride have been shown singly and in combination to affect the distribution of CEA titers in populations (9).

CEA titer analysis was included in the Environmental Sciences Laboratory's protocol for evaluation of the health status of PBB-exposed Michigan farm residents.

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# Materials and Methods

## Population

Farm family units as well as families which had purchased farm produce directly from these farms were invited to participate voluntarily in the survey conducted November 4–11, 1976 in Grand Rapids, Michigan. Individuals from quarantined and non-quarantined farms were selected in a statistically random manner. A subgroup of self-selected farmers were also examined. A detailed discussion of the selection methods is described by Anderson et al. (10).

A comparison group of non-PBB-exposed families which would have the same general farm environmental exposures except for PBB was sought. A comparable group of Wisconsin dairy farmers was identified and examined.

## Examination Protocols

History of current and past medical illness, cigarette use, and current alcohol consumption were obtained by a physician at the time of examination.

Included in the battery of laboratory studies performed for adults (age 18 and over) was the CEA-Roche titer (6). Sample collection and storage materials were those supplied by Hoffmann-LaRoche, Inc. A 4-ml portion of EDTA plasma was frozen and later transported to the company laboratories in their Nutley, New Jersey research facility, where sample analysis was performed without knowledge as to the identity of the samples. The radioimmunoassay used had a sensitivity of  $\pm 0.5$  ng/ml. Using this method, Hoffmann-LaRoche reports that 97% of normal, healthy, nongarette smoking adults have titers below 2.5 ng/ml (6).

Serum PBB analyses were performed using the methods and procedures described by Wolff et al. (11).

## Statistics

A  $2 \times 2$  chi-square test was used to test the significance of differences in the prevalence of elevated CEA titers in the populations studied.

## Results

CEA titers were obtained on 611 of 626 adults in the Michigan group, and 138 of the 156 adults in the Wisconsin group. Table 1 summarizes the overall distribution of CEA titers in the two populations.

Table 1. Distribution of CEA titers in the two populations tested.

Study group	Total tested	CEA 0–2.5 ng/ml		CEA 2.6–5.0 ng/ml		CEA 5.1–10 ng/ml		CEA > 10 ng/ml	
		No.	%	No.	%	No.	%	No.	%
Michigan	611	536	87.7	55	9	16	2.6	4	0.7
Wisconsin	138	129	93.5	8	5.8	1	0.7	0	0

Although the prevalence of titers greater than 2.5 ng/ml is higher in the Michigan group than the Wisconsin one, the differences are not significant.

The possible effects of age on the titer distribution is examined in Table 2. A trend toward a greater prevalence of elevated titers in the older age categories is present in both the Michigan and Wisconsin groups. There is no statistically significant difference among the Wisconsin age categories. The Michigan "less than 36 years of age" category has a significantly lower prevalence of elevated titers than either of the other age categories (respectively,  $\chi^2 = 6.1, p < 0.02$ ,  $\chi^2 = 5.1, p < 0.02$ ).

In Table 3, the distribution of CEA titers by sex is summarized. In both populations, males had a higher prevalence of elevated titers than females. This difference is highly significant for the Michigan group ( $\chi^2 = 16.1, p < 0.001$ ).

In the collaborative study of Hansen et al. (6), cigarette smoking was shown to affect CEA titer distribution. We analyzed the results in the Michigan and Wisconsin groups in relation to their cigarette smoking habits. Table 4 summarizes the comparison. In both groups, current cigarette smokers had a significantly higher prevalence of elevated CEA titers than nonsmokers (Michigan  $\chi^2 = 40.7, p < 0.001$ , Wisconsin  $\chi^2 = 11.3, p < 0.001$ ). Former smokers fell between the other categories. In the two populations, former smokers were not significantly different from the nonsmokers. Within smoking categories, the Michigan and Wisconsin populations did not differ.

Heavy alcohol consumption and alcoholic cirrhosis are associated with elevated CEA titers (7). Seven individuals in our survey population regularly consumed more than one quart of whisky or its equivalent per week. Six of the seven had normal CEA titers. Removal of the one individual result (between 2.5 and 5 ng/ml) does not affect the results of the analysis.

Previous history of, or currently active disease, can cause elevations in the CEA titer (5). Table 5 groups the Michigan examinees by whether or not they had ever been treated for inflammatory bowel disease, ulcers, polyps, chronic lung disease, liver disease, or malignancies. Individuals with histories

Table 2. CEA titer distribution among Michigan and Wisconsin farmers by age.

Age, years,	Group	Total examined	CEA 0-2.5 ng/ml		CEA 2.6-5 ng/ml		CEA 5.1-10 ng/ml		CEA > 10.1 ng/ml	
			No.	%	No.	%	No.	%	No.	%
18-35	Michigan	286	262	91.5	20	7	4	1.5	0	0
	Wisconsin	32	32	100	0	0	0	0	0	0
36-55	Michigan	228	193	84.6	22	9.6	10	4.4	3	1.3
	Wisconsin	73	67	92	5	7.5	1	1.5	0	0
36+	Michigan	97	81	83.5	13	13.4	2	2.1	1	1.0
	Wisconsin	34	31	91	3	9	0	0	0	0

Table 3. Distribution of CEA titers among Michigan and Wisconsin farmers by sex.

Sex	Group	Total examined	CEA 0-2.5 ng/ml		CEA 2.6-5 ng/ml		CEA 5.1-10 ng/ml		CEA < 10.1 ng/ml	
			No.	%	No.	%	No.	%	No.	%
Males	Michigan	312	265	84.9	36	11.5	8	2.6	3	1.0
	Wisconsin	76	70	92.1	5	6.6	1	1.3	0	0
Females	Michigan	299	271	90.6	19	6.4	8	2.7	1	0.3
	Wisconsin	62	59	95.2	3	4.8	0	0	0	0

Table 4. Distribution of CEA titers among Michigan and Wisconsin farmers by current cigarette use.

Cigarette use	Study group	Total examined	CEA 0-2.5 ng/ml		CEA 2.6-5 ng/ml		CEA 5.1-10 ng/ml		CEA > 10.1 ng/ml	
			No.	%	No.	%	No.	%	No.	%
Never smoked cigarettes	Michigan	355	332	93.5	19	5.4	4	1.1	0	0
	Wisconsin	97	94	96.9	3	3.1	0	0	0	0
Former cigarette smokers <sup>a</sup>	Michigan	103	91	88.4	8	7.8	2	1.9	2	1.9
	Wisconsin	25	23	92.0	2	8.0	0	0	0	0
Current cigarette smokers	Michigan	147	107	72.8	28	19.0	10	6.8	2	1.4
	Wisconsin	16	12	75.0	3	18.8	1	6.2	0	0

<sup>a</sup> Ceased smoking more than one year ago.

Table 5. Distribution of CEA titers among Michigan farmers by past history of medical illness.

Past medical history	Total examined	CEA 0-2.5 ng/ml		CEA 2.6-5 ng/ml		CEA 5.1-10 ng/ml		CEA > 10.1 ng/ml	
		No.	%	No.	%	No.	%	No.	%
Negative	445	401	90.1	35	7.9	8	1.8	1	0.2
Positive <sup>a</sup>	166	135	81.3	20	12.0	8	4.8	3	1.8

<sup>a</sup> One or more of the following present in the past medical history: chronic bronchitis and/or emphysema; gastrointestinal disease, ulcers, inflammatory bowel disease, polyps history of malignancy; other: cirrhosis, gall bladder disease, thyroid. The prevalence of elevated CEA titers was significantly higher in the group with positive past medical history ( $\chi^2 = 8.7, p < 0.01$ ).

of such disorders had a significantly higher prevalence of elevated CEA titers compared with those without history of such diseases ( $\chi^2 = 8.7, p < 0.01$ ). Examining the combined effect of current cigarette smoking and abnormal medical histories, 16 of 54

(30%) had elevated CEA titers while in the nonsmoker-normal medical history group, only 16 of 282 (6%) had elevated titers. A combined effect of cigarette smoking and abnormal medical history is clearly evident.

Table 6. Distribution of CEA titers in relation to serum PBB levels.

Serum PBB level, ppb	Total tested	CEA 0-2.5 ng/ml		CEA 2.6-5.0 ng/ml		CEA 5.1-10 ng/ml		CEA > 10 ng/ml	
		No.	%	No.	%	No.	%	No.	%
Nondetected-0.2	16	16	100	0	0	0	0	0	0
> 0.2-1.0	67	59	88	5	7.5	2	3.0	1	1.5
> 1.0-5.0	168	149	88.7	15	8.9	3	1.8	1	0.6
> 5.0-10.0	53	49	92.4	3	5.7	1	1.9	0	0
≥ 10.0	58	43	74.1	11	19.0	3	5.2	1	1.7

Table 7. Distribution of CEA titers in smokers in relation to serum PBB levels less than and greater than 10 ppb.<sup>a</sup>

Serum PBB level, ppb	Total tested	CEA 0-2.5 ng/ml		CEA 2.6-5.0 ng/ml		CEA 5.1-10 ng/ml		CEA > 10 ng/ml	
		No.	%	No.	%	No.	%	No.	%
< 10	83	63	75.9	14	16.9	5	16.0	1	1.2
≥ 10	17	8	47.1	6	35.4	2	11.8	1	5.9

<sup>a</sup> The prevalence of abnormal CEA titers (> 2.5 ng/ml) is significantly greater in smokers ( $\chi^2 = 5.70$ ,  $p < 0.02$ ) with serum PBB levels greater than or equal to 10 ppb.

Of the 611 Michigan adults whose CEA titers have been estimated, 362 have at this time had their serum PBB concentrations determined. While selection of samples for PBB analyses were randomized, caution must be exercised in drawing conclusions prior to the availability of all results. Table 6 shows the distribution of CEA titers by serum PBB levels. The prevalence of elevated CEA titers is significantly greater among individuals with higher serum PBB levels ( $\chi^2 = 13.0$ ,  $df = 4$ ,  $p < 0.02$ ). The largest incremental change occurred at the 10 ppb serum PBB concentration.

We investigated the possible multiple factor interaction of serum PBB levels and cigarette smoking. Table 7 demonstrates that cigarette smokers with serum PBB levels above 10 ppb have significantly higher prevalence of elevated CEA titers than cigarette smokers with lower serum PBB concentrations ( $\chi^2 < 5.7$ ,  $p < 0.02$ ).

## Discussion

CEA titers were determined for 611 Michigan farmers exposed to PBB and a control population of 138 Wisconsin farmers. The overall prevalence of elevated titers was slightly higher in the Michigan study group than in Wisconsin, but the difference did not approach statistical significance.

The results of this study are consistent with the findings of other investigators. CEA titers may be influenced by many different factors singly or in combination. As others have found, cigarette smoking and current and past medical illnesses can

significantly affect CEA titer distribution. Interpretation of individual titers must consider such factors. These principally affect CEA titer elevations in the lower titer ranges (< 10 ng/ml), and such levels should not be considered diagnostic of malignancy.

Of the four individuals in our survey with titers greater than 10 ng/ml, one was subsequently diagnosed as having a neoplasm and one had a recurrence of a previously diagnosed malignancy. The other two are under observation.

The relationship of various population characteristics of CEA titer distribution was investigated. Comparing the groups by sex and age categories did not show any significant differences, although males in each group had higher prevalence of elevated titers. The sex difference was, overall, more pronounced in the Michigan population and reached a  $p < 0.001$  level of significance. Multiple factors were probably responsible for this difference. Males tended to have a higher prevalence of cigarette smoking, and when they smoked, did so more heavily. Wolff et al. (11) found serum PBB concentrations to be higher among males tested. Further, as demonstrated here, serum PBB affects CEA titer and is additive to the effect of smoking. It is also interesting to note that elevations of SGPT were significantly more prevalent among Michigan males than females (12). Further investigation of these interrelationships will follow the completion of serum and fat biopsy PBB analyses.

Age differences were also noted in both the Michigan and Wisconsin examined populations. One consideration which may be related to this

finding would be that younger individuals have fewer current medical problems, and if they smoke cigarettes, have not smoked for as long a period.

Examining available data concerning serum PBB concentrations, it appears there is an association between CEA titers and serum PBB, and that the effects of serum PBB are additive to other factors discussed. Until completion of analysis of all specimens, however, judgment on the significance of this initial observation should be held in abeyance.

CEA titer distribution appears to be associated with general health status as reflected by the factors reviewed and known to be associated with disease. Environmental agents such as cigarette smoke, PBB, and occupational exposure to vinyl chloride also influence titer distribution, although the mechanisms by which various agents do this need further study. Serial studies of CEA titers in the PBB-exposed farmers, and prospective observation will allow further assessment of whether individuals with elevated titers have a different health experience than those with lower titers.

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